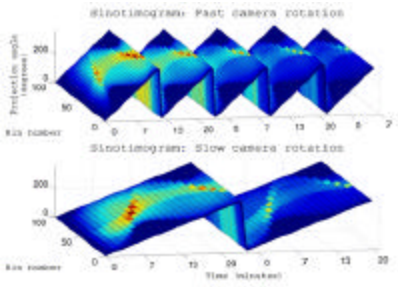
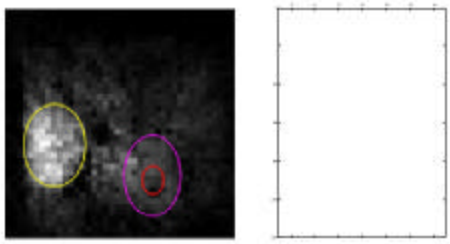
Reconstruction Algorithms for Dynamic Imaging



Algorithms: making movies with SPECT ^{99m}Tc-teboroxime reconstruction



EECS C145B / BioE C165: Image Processing and Reconstruction Tomography

Lecture 13

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Lecture material due to Bill Moses and Greg Klein, LBNL.

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Fundamentals of Medical Imaging

PET

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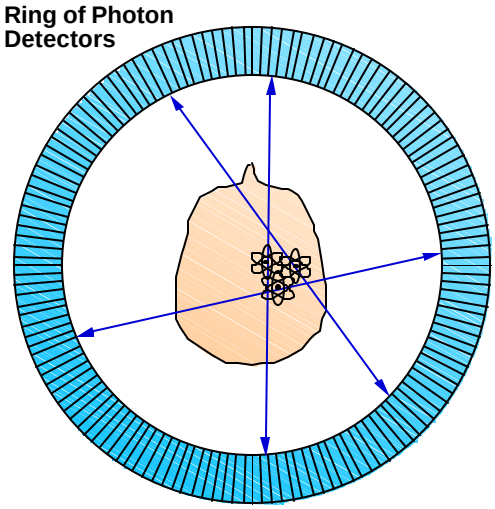
Lawrence Berkeley National Laboratory

Outline:

- **Fundamentals of PET**
- **Basic Detector Design**
- **Real World Considerations**
- **Performance Evaluation**
- **Tracer Isotopes**
- **Clinical Uses**

How Does PET Work?



- **Patient injected with drug having β^+ emitting isotope.**
- **Drug localizes in patient.**
- **Isotope decays, emitting β^+.**
- **β^+ annihilates with e^- from tissue, forming back-to-back 511 keV photon pair.**
- **511 keV photon pairs detected via time coincidence.**
- **Positron lies on line defined by detector pair (a *chord*).**

Forms Planar Image of a "Slice" Through Patient

PET stands for positron emission tomography. Like SPECT, the patient is injected with a biologically active, radioactively labeled drug. The drug then localizes somewhere in the patient, and the radioisotope decays, but unlike SPECT, it emits a positron (hence the name) which is stopped in the tissue and annihilates with an electron to form two back-to-back photons. These photons pass through the patient and are detected, producing an image of the drug concentration using computed tomography.

A typical PET camera consists of a planar ring of small photon detectors, with each photon detector placed in time coincidence with *each* of the individual photon detectors on the other side of the ring. When a pair of photon detectors simultaneously detect 511 keV photons, then you know that a positron decayed somewhere on the line connecting the two detectors. This line is known as a *chord*, and the method of using time coincidence between two detectors (rather than a collimator and one detector) to restrict events to a line is known as electronic collimation.

I will assume that you now know how an image is reconstructed, given all the projections of that image (*i.e.* the count rate in each chord).

Difference Between PET and SPECT:

Radioactive label is a positron (not single photon) emitter.

From a Machine Builder's Viewpoint:

+ Don't need a collimator (higher detection efficiency).

– Must detect a pair of photons (electronics more difficult).

PET is very much like SPECT, except that it uses a positron emitting (rather than single photon emitting) radioactive label. From a machine builder's viewpoint, this means that you don't need the (very inefficient) photon collimator that you need with SPECT, but the electronics is more difficult as you need to detect "pairs" rather than "singles."

Why bother with PET? Why not just use SPECT? There are four main reasons:

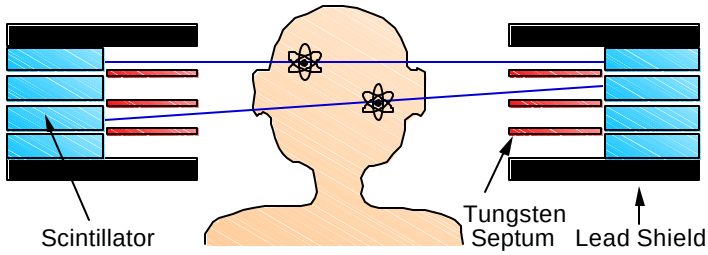
(1) Electronic collimation is more efficient than lead collimators, so the signal to noise for a give patient dose is greater.

(2) The spatial resolution is usually better.

(3) You can more quantitatively measure the tracer uptake (SPECT is mostly qualitative).

(4) Most importantly, the tracers are chemically different, so drugs that can "see" things that can't be seen with SPECT can be used.

Multi-Layer PET Cameras



+ Can image several slices simultaneously.
+ Can image cross-plane slices.
+ Can remove septa to increase efficiency ("3-D PET")

– More expensive.

Planar Images "Stacked" to Form 3-D Image

Most modern PET cameras consist of several of these planar rings stacked on top of each other to form a multi-layer system, as shown above. This allows several parallel images (known as slices) to acquired simultaneously, and also allows additional images to be acquired with cross-plane slices. The lead shields prevent activity from the patient from causing spurious counts in the tomograph ring, while the tungsten septa provides partial collimation to reject some of the events in which one (or both) of the 511 keV photons suffer a Compton scatter in the patient. These septa are often removable to acquire *"fully 3-D"* data – removing the septa significantly increases the efficiency for detecting both "true" coincidences and Compton scattered events.

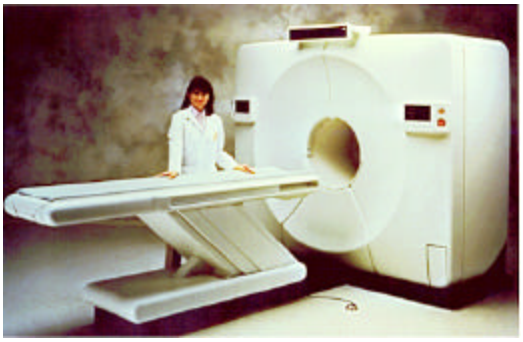
It is possible to move the patient through the scanner a section at a time, stopping to acquire an image at each section. These sections can be reconstructed and displayed next to each other to for a *whole body image* of a patient.

Typical Tomograph Parameters

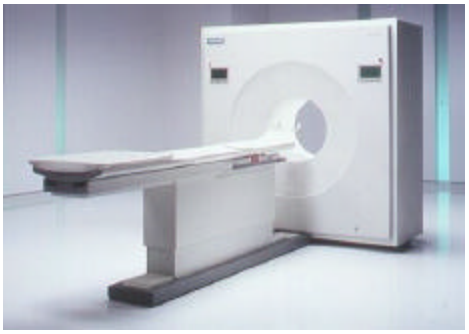
- **Patient port 30 cm diameter (head machine) or 50 cm diameter (body machine).**
- **3.5 to 6 mm scintillator crystal width.**
- **24 to 48 layers, covering 15 cm axially.**
- **8 liters of BGO scintillator crystal.**
- **500 photomultiplier tubes.**
- **"Several" million dollars**
  - **Scintillator is 25% of total parts cost**
  - **PMTs are 25% of total parts cost**
  - **Next component is <5% total parts cost**

I would like to give you an order of magnitude estimate of the typical ring parameters in a modern PET camera, realizing that there are many variations. Most cameras are designed to image either the brain or the heart, with the main difference being the size of the patient port. Brain machines usually have a 30 cm diameter patient port, while heart machines (also known as whole body machines) usually have a 50 cm diameter patient port. Modern PET cameras usually have between 200 and 700 detector elements per layer, with 512 elements per layer being particularly popular. The number of layers ranges from one to forty-eight, and the cost for a PET camera is several million dollars.

PET Cameras



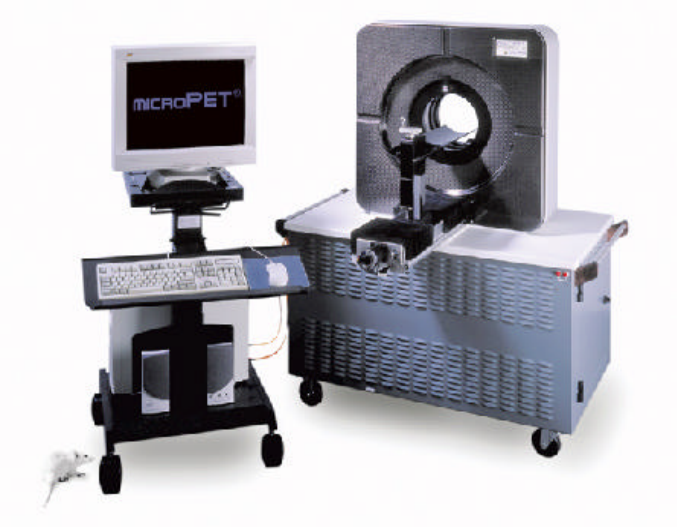
General Electric



Siemens / CTI

Here are pictures of typical commercial PET cameras. The patient usually lies down on the bed, and the imaging planes are oriented perpendicular to the floor.

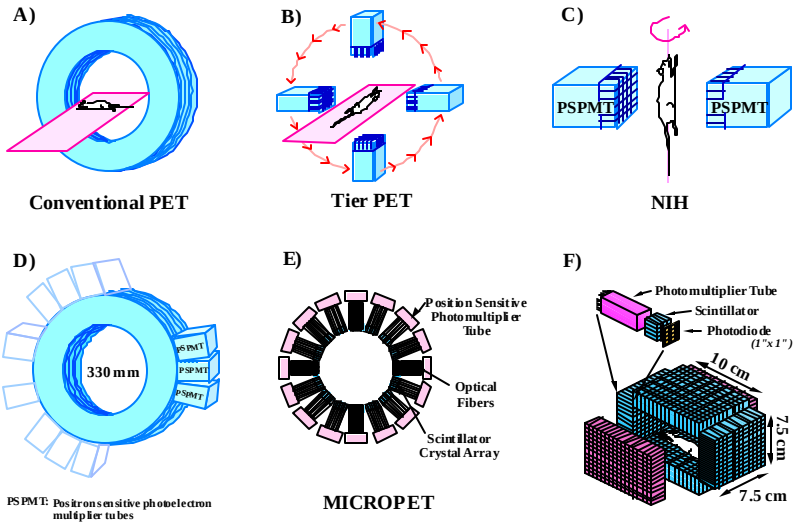
PET Cameras

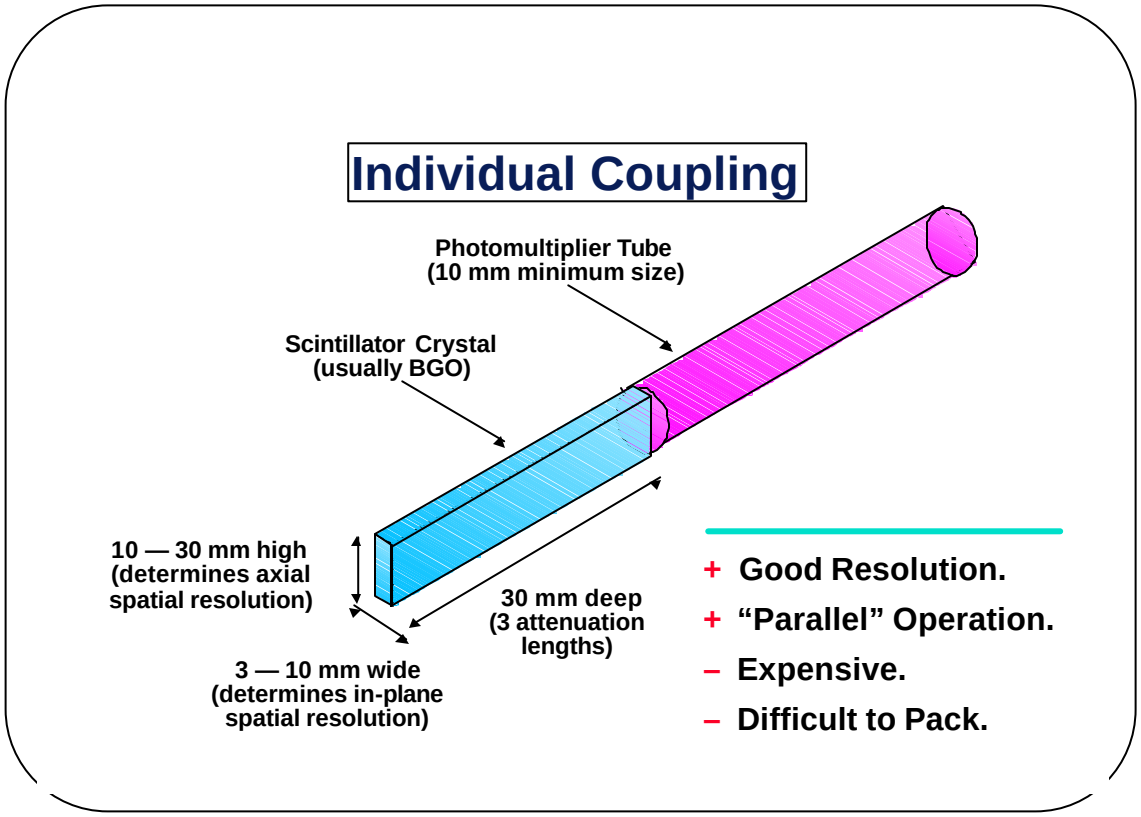


Concorde Microsystems

The MicroPET system was originally developed at UCLA for imaging small animals. Such systems can be used, for example, to image gene expression in transgenic mice.

Hardware: Evolution of PET

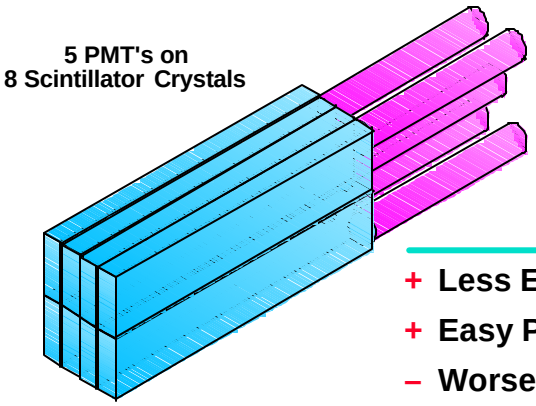


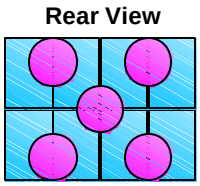


The most obvious way to make a 511 keV photon detector is to individually couple photomultiplier tubes to a heavy scintillator crystal, usually BGO. The width of the crystal is usually between 3 and 10 mm, and this width determines the in-plane spatial resolution of the camera (more on this later). The height of the crystal is usually between 10 and 30 mm, and determines the thickness of the plane that you image, and hence the axial resolution. Notice that if the size of the object that you wish to image is thinner than this imaging plane (or is not uniform through the thickness of the plane), you will get an inaccurate measurement of the activity in that object. This is known as the partial volume effect. Finally, almost all cameras have 30 mm deep scintillation crystals – this is determined by the attenuation length of 511 keV photons in BGO.

This "individually coupled" design is capable of very high resolution, and since the design is very parallel (all the photomultiplier tubes and scintillator crystals operate independently), is capable of very high throughput. The disadvantages of this type of design are that it requires a lot of photomultiplier tubes, and thus is expensive, and that connecting round photomultiplier tubes to rectangular scintillation crystals leads to problems packing the crystals to form a solid ring.

Block Design



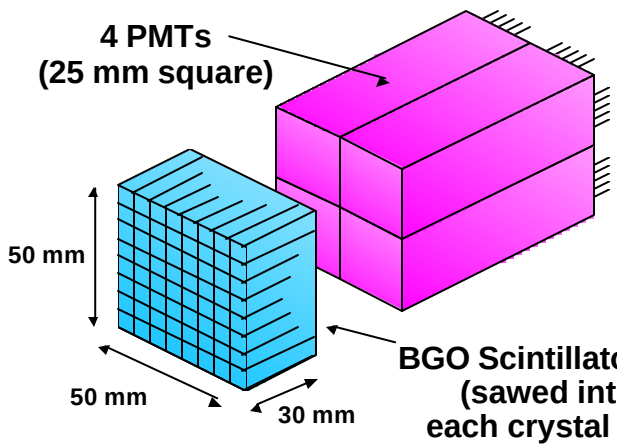


+ **Less Expensive.**
+ **Easy Packing.**
– **Worse Resolution.**
– **More Dead Time.**
– **More Complicated Electronics.**

The more common way to make a 511 keV photon detector is use what is called a block detector design. A block detector couples several photomultiplier tubes to a bank of scintillator crystals, and uses a coding scheme to determine the crystal of interaction. In the two layer block shown above, five photomultiplier tubes are coupled to eight scintillator crystals. Whenever one of the outside four photomultiplier tubes fire, you know that a 511 keV photon interacted in one of the two crystals attached to that photomultiplier tube, and the center photomultiplier tube is then used to determine whether it was the inner or outer crystal. This is know as a "digital" coding scheme, as each photomultiplier tube is either "hit" or "not hit," and the crystal of interaction is determined by a "digital" mapping of the hit pattern.

"Block detector" designs are much less expensive and much easier to form into a multi-layer camera. However, errors in the decoding scheme reduce the spatial resolution, and since the entire block is "dead" whenever one of its member crystals is struck, the dead time is worse than with individual coupling. Finally, additional electronics is necessary to decode the output of the block.

Block Design Using Anger Logic



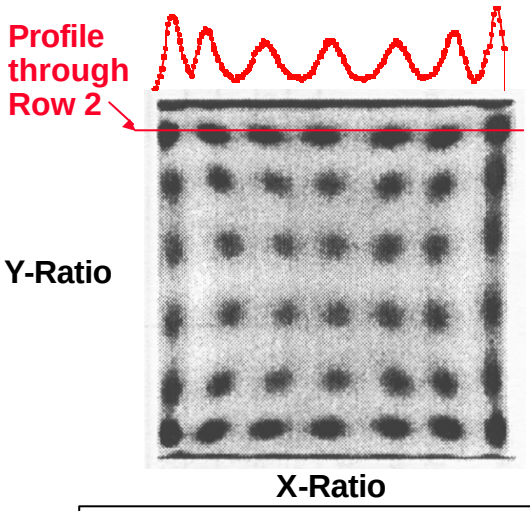
- Saw cuts direct light toward PMTs.
- Depth of cut determines light spread at PMTs.
- Crystal of interaction found with Anger logic (i.e. PMT light ratio).

Good Performance, Less Expensive, Easy to Pack

Most block detector coding schemes use an "analog" coding scheme, where the ratio of light output (*i.e.* Anger logic) is used to determine the crystal of interaction. In the example above, 4 photomultiplier tubes are coupled to a block of BGO that has been partially sawed through to form 64 "individual" crystals. The depth of the cuts are critical – deep cuts tend to focus the scintillation light onto the face of a single photomultiplier tube while shallow cuts tend to spread the light over all four photomultiplier tubes.

This type of coding scheme is more difficult to implement than digital coding, as analog light ratios place more stringent requirements on photomultiplier tube linearity and uniformity, as well as scintillator crystal uniformity. However, most commercial PET cameras use an analog coding scheme since it is much less expensive due to the fewer number of photomultiplier tubes required.

Crystal Identification with Anger Logic



- Uniformly illuminate block.
- For each event, compute X-Ratio and Y-Ratio, then plot 2-D position.
- Individual crystals show up as dark regions.
- Profile shows overlap (i.e. identification not perfect).

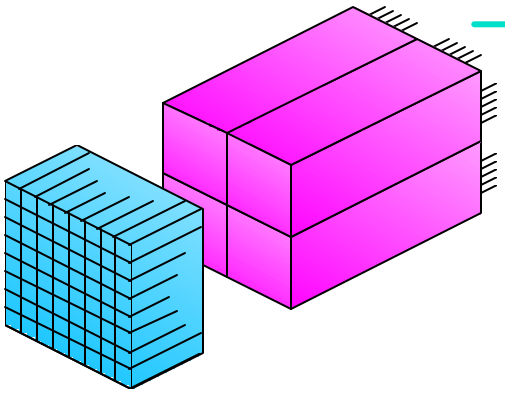
Can Decode Up To 64 Crystals with BGO

This figure shows the decoding pattern in a 7 x 8 crystal block detector. The entire block is uniformly illuminated with 511 keV photons, and whenever an interaction is detected, the X and Y position estimators are computed and plotted on this 2-D scatter plot. The dark regions in the plot show the positions of the individual crystals in this ratio space, and show that the ability to decode crystals is generally quite good.

However, the decoding is not perfect! Due to the limited light output of BGO, less than 200 photoelectrons are produced with each 511 keV interaction. As the profile shown above shows, statistical fluctuations broaden the individual peaks so that the tails of the distributions for adjacent crystals overlap. The amount of overlap is almost exactly what is predicted based on fluctuations due to counting statistics.

Detector Requirements

Detect 511 keV Photons With (in order of importance):



- **>85% efficiency**
- **<5 mm spatial resolution**
- **"low" cost (<$100 / cm^2)**
- **"low" dead time (<1 μs cm^2)**
- **<5 ns fwhm timing resolution**
- **<100 keV energy resolution**

Based on Current PET Detector Modules

There are a number of requirements that a PET detector module must satisfy. The most important is that it detect 511 keV photons with high efficiency, as PET is essentially starved for statistics. It must localize the position of interaction to better than 5 mm in order to provide acceptable spatial resolution. The cost must be less than $100 per cm^2 of front surface area in order to be cost competitive. It must have a low dead time figure of merit (detector module dead time times front surface area), provide a sufficiently accurate timing signal, and acceptable energy resolution.

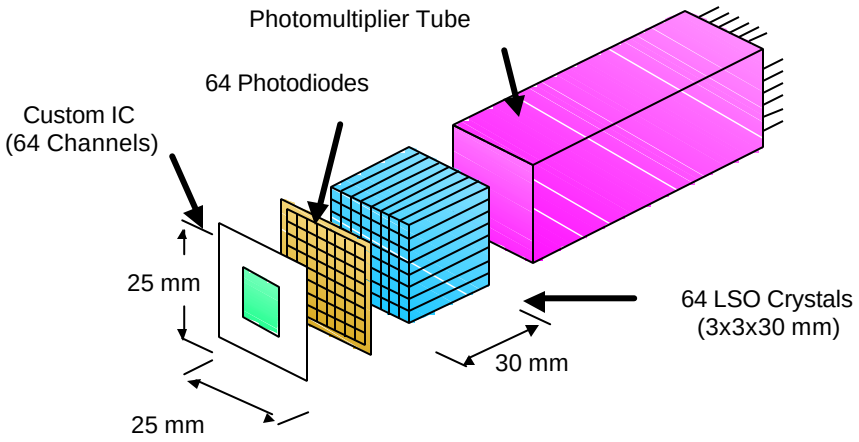
Current Trends: LSO Scintillator

	BGO	LSO
Formula	$Bi_4Ge_4O_{12}$	Lu_2SiO_5:Ce
Atten. Len.	1.1 cm	1.2 cm
Photo Fract.	43%	34%
Photon/MeV	8,200	25,000
Decay Time	300 ns	40 ns
Emission l	480 nm	415 nm
Radioactive?	No	Yes
		(300 dps/cc)

Many New Detector Designs Based on LSO

The performance of a PET detector module is mainly determined by the scintillator. The relatively recently discovered scintillator LSO (cerium doped lutetium orthosilicate) has properties that are nearly ideal for PET. It has similar stopping power to BGO, but with significantly higher light output and shorter decay time. This alters the tradeoffs imposed on detectors, and has lead to many new LSO based design proposals, most of which have significantly higher performance than BGO based designs. While LSO is presently difficult to obtain, BGO was also quite difficult to obtain shortly after its discovery and it is now quite available. LSO is capable of being grown in "large" boules (such as the 3" diameter ones shown in the above photograph), and so I expect that it too will become readily available and a commonly used scintillator for PET.

LBNL Detector Module Design



- PMT Provides Timing Pulse and Energy Discrimination
- PD Array Identifies Crystal of Interaction
- PD+PMT Measures Energy Deposit
- PD / (PD+PMT) Measures Depth of Interaction

Moses et al., LBNL

Coincidence Circuit Requirements

- **Good time resolution (10-20 ns).**
- ***Lots* of chords (~280,000,000 in 48 layer camera with septa removed).**
- **High event rate (5,000,000 / second).**

Parallel Electronics is Necessary

The coincidence circuitry must be able to determine coincident events with 10 to 20 ns resolution for each crystal-crystal combination (*i.e.* chord). The timing requirement is set jointly by the time-of-flight across the detector ring (4 ns) and the BGO-BGO resolving time (typically 3 ns). The most stringent requirement, however, is the vast number of chords in which coincidences must be determined – approximately 6 million in a 48 layer camera with septa in place and 280 million with the septa removed!

It is obviously impractical to have an individual coincidence circuit for each chord, so tomograph builders use parallel organization to solve this problem. A typical method is to use a high speed clock (typically 500 MHz) to mark the arrival time of each 511 keV photon and a digital coincidence processor to search for coincident pairs of detected photons based on this time marker. This search can be done extremely quickly by having multiple sorters working in parallel. Custom integrated circuits are frequently used for this task.

Computer Readout

Originally, computer memory was slow and expensive:

- **Dedicated histogramming modules.**
- **List mode readout.**
- **CAMAC type interface.**

Today, computer memory is fast and cheap:

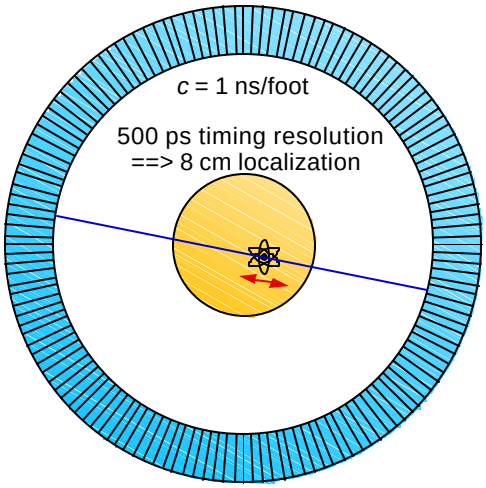
- **Direct memory access.**
- **VME type interface.**
- **Custom VLSI.**

Must histogram 280,000,000 chords at 5 MHz

The computer must be able to histogram up to 280 million chords (*i.e.* determine how many counts are in each chord) as they are detected by the camera at a rate of up to 5 MHz. In the old days, computer memory was slow and expensive, so dedicated hardware modules were built (usually CAMAC based) to do the histogramming. Alternatively, designers resorted to "list mode" readout, in which the identity of each chord was sequentially written to disk on an event by event basis, resulting in a long list of events that was processed later to form a histogram.

Today, computer memory is fast and cheap, so the histogramming is done in real-time directly in computer memory, often with a VME based system or in custom VLSI circuits.

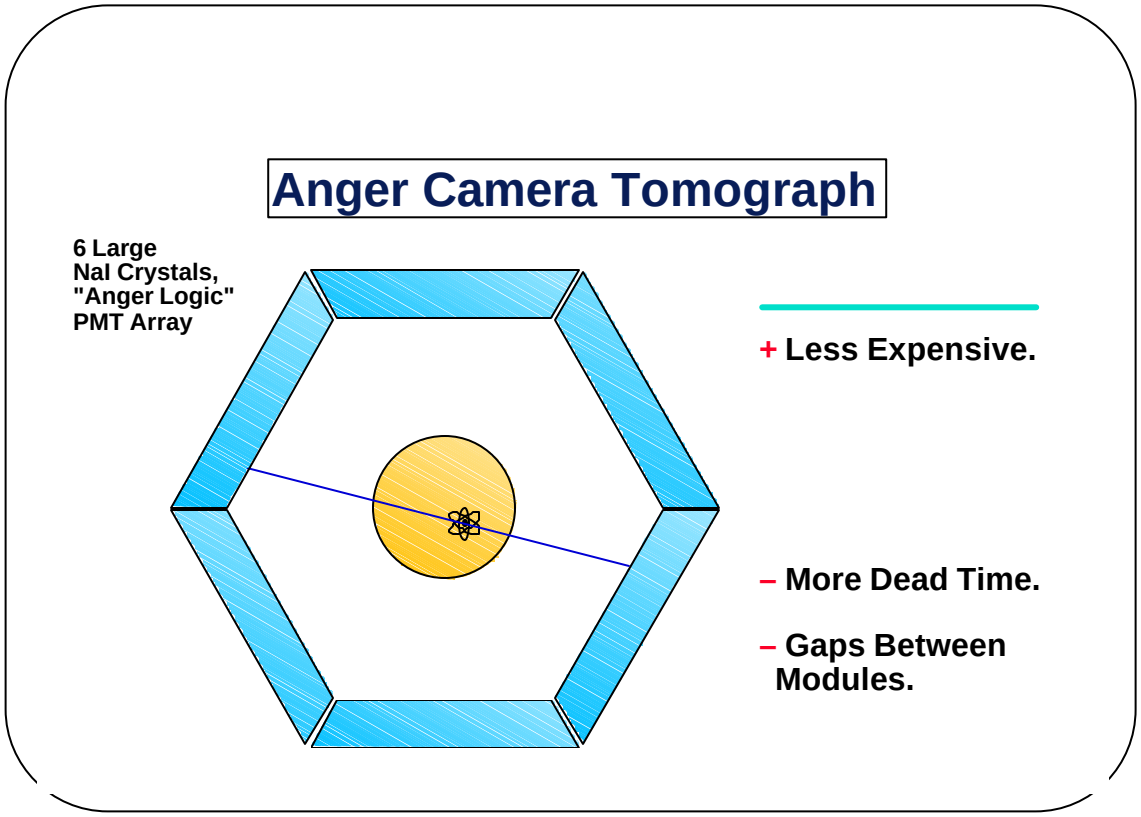
Time-of-Flight Tomograph



- **Can localize source along line of flight.**
- **Time of flight information reduces noise in images.**
- **Time of flight tomographs have been built with BaF_2 and CsF.**
- **Difficult to keep all detectors in accurate time coincidence.**

One normal variation in PET cameras is the “time-of-flight” design. By measuring the difference in arrival time at the two detectors, the positron source can be localized along the line of flight. Doing this reduces the volume that the isotope is localized in, and so improves the signal to noise ratio. Current state of the art with these systems is 500 ps timing resolution with barium fluoride scintillators, which results in 8 cm localization, which is only about half the size of the human head. The net result is a tomograph with a slightly better signal to noise in the resulting image than with a BGO tomograph.

Some additional problems arise from the use of barium fluoride as a scintillator. It is less dense than BGO, and so the spatial resolution is degraded. In addition, the wavelength of its fast emission is in the hard UV, which makes it difficult to work with (*i.e.* expensive) because it does not penetrate glass-windowed photomultiplier tubes or any known glue (to couple the crystal to the photomultiplier tube). Finally, it is difficult to keep these cameras in tune.



Another normal variation is the “Anger camera” design, where the ring is composed of a series of planar, sodium iodide Anger cameras. This is effectively the block design concept taken to the extreme, and so it has the same advantages and disadvantages as a block design. It is less expensive than conventional designs, but the dead time (and maximum event rate) is greatly compromised. Sodium iodide scintillator must be used in order to get enough light output to do the Anger logic, but this scintillator is less dense than BGO, and so the spatial resolution is also degraded. A final problem is the gap between detector modules (sodium iodide is hygroscopic, and must be in sealed cans), which can give the reconstruction algorithms problems.

Real World Effects

- **Attenuation**
- **Random Coincidences**
- **Scatter**
- **Radial Elongation**

Thus far I have described the operation of a PET camera in the ideal world. There are several real world effects that limit the performance of these cameras or require that corrections be made.

Attenuation

- **Attenuation length of 511 keV photons in water (*i.e.* tissue) is 10 cm.**
- **Brain is 20 cm diameter.**

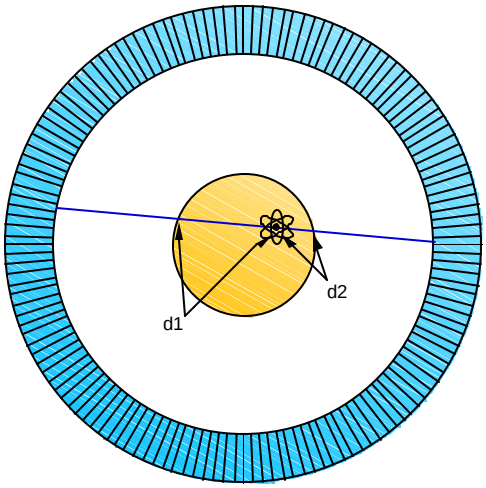
==> **up to e^{-2} = 86% of the events are lost.**

- **Loss fraction depends on position in patient.**

==> **Need to correct for attenuation.**

The largest problem is the attenuation of the 511 keV photons *inside* the patient, which can cause up to 86% of the events to be lost. This attenuation is position dependent, and so cannot be accurately modeled or estimated. Unlike SPECT, this effect can be accurately measured and corrected for in PET on a chord by chord basis, allowing quantitative studies to be performed.

Attenuation of Internal Source



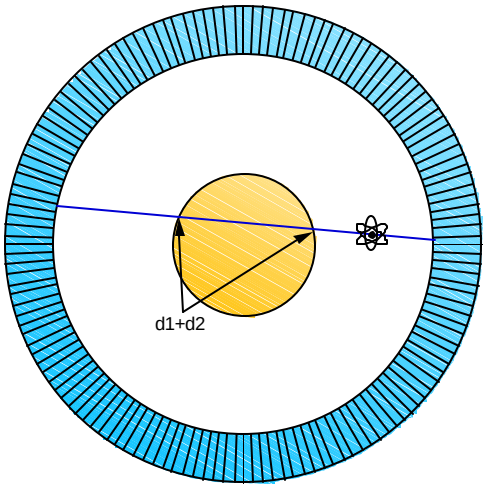
$$P_1 = e^{-\frac{d1}{l}} \qquad P_2 = e^{-\frac{d2}{l}}$$

$$P = e^{-\frac{d1+d2}{l}}$$

Event detection probability is product of individual photon detection probabilities.

The attenuation correction is performed as follows. Consider a positron source inside a uniform attenuator. The probability that the first photon escapes to be detected is given by the expression for P_1, while the probability that the second photon escapes to be detected is given by the expression for P_2. The event detection probability is the product of these two probabilities (as the two photon detections are independent), and is given by the expression for P.

Attenuation of External Source



$$P = e^{-\frac{d1+d2}{l}}$$

Same attenuation as internal source.

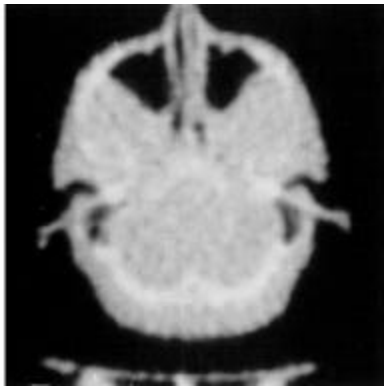
==> **Can use attenuation from external source to correct internal source data.**

Now consider a positron source outside the uniform attenuator, but one that would excite the same chord as in the previous example. The probability that the first photon penetrates the absorber and is detected is given by the expression for *P*, while the probability that the second photon is detected is unity (there is no absorber between it and the detector). Therefore, the event detection probability is just *P*, which is the same as for the internal source. In reality, our absorbers are not uniform, but this merely means that the simple exponential expression turns into a line integral, but the result remains the same: the event detection probability is *independent* of the position of the positron emitter on the line.

This attenuation measurement is done for all chords using either a hoop containing uniform activity or an orbiting positron source, and is called a *transmission* scan. This same hoop or orbiting source can also be used, after removing the absorber (*i.e.* the patient) to correct for individual crystal / chord efficiencies – this is frequently referred to as a *hoop* or *blank* scan.

The detector dead time places severe limits on the transmission scan. The transmission source produces very high singles rates (~1 MHz) in the detector modules closest to it. Significantly higher source strengths (10x – 100x) are greatly desired in order to reduce the time taken for the scan, but detector dead time will not allow any increase in activity.

Transmission Scan

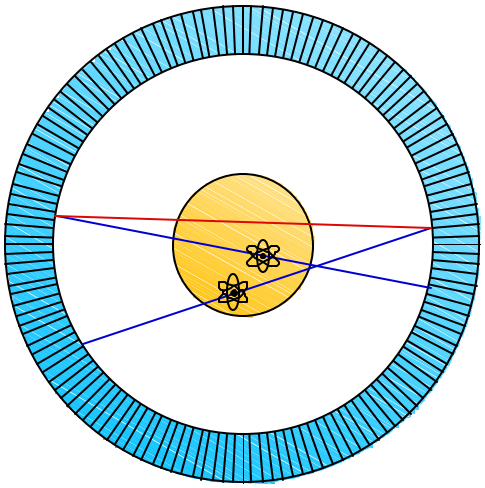


XBB 887-6863

- **Can reconstruct an image of the attenuation**
- **Essentially a 511 keV x-ray CT image.**

This chord by chord attenuation measurement that we have just done represents the same information that is collected in an x-ray CT scan, except the "x-ray" energy is 511 keV. This information can be reconstructed, forming images such as the ones above. The physiological features shown in these images can even be used to help position the patient.

Random Coincidences



- **Simultaneous decays can cause erroneous coincident events called Randoms.**
- **For 3-D PET, randoms can be as high as 50% of image.**
- **Random Rate is $Rate_1 \times Rate_2 \times 2\Delta t$**
- **Randoms reduced by narrow coincidence window Δt.**
- **Time of flight across tomograph ring requires $\Delta t > 2$ ns.**

Simultaneous decays can cause random coincident “events” that must be corrected for. They can be reduced by using as narrow a coincident timing window as possible, but cannot be reduced below 2 ns due to time of flight considerations. Randoms can be corrected for (on a chord by chord basis) by measuring the random event rate. This measurement is usually done by measuring the singles rates for all crystals. Since these random events are uncorrelated in time, the random coincident rate for a give chord is just the product of the singles rates for its two crystals times twice the coincidence window width.

What Is Actually Reconstructed?

3 Scans Taken:

- **Hoop (external source with nothing in ring).**
- **Transmission (external source with patient in ring).**
- **Emission (patient after isotope injected).**

Recon. = (Emission – Randoms) / Attenuation / Efficiency

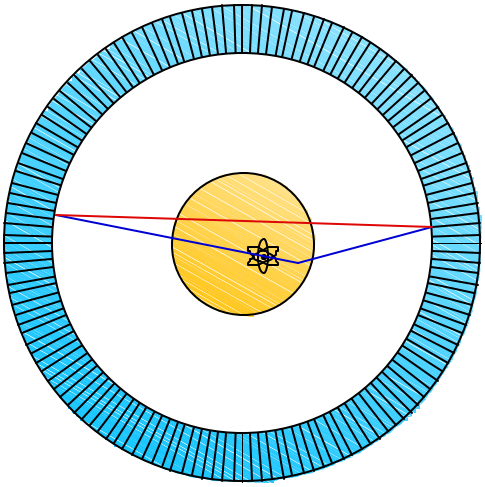
Attenuation = Transmission / Hoop

Efficiency = Hoop / Hoop_Average

These two effects, attenuation and random coincidences, as well as the individual chord efficiency, can be corrected for on a chord by chord basis and are the only corrections applied in a routine clinical study.

The data that is actually reconstructed is collected as follows. A hoop scan is acquired, and from it the efficiency for each chord is computed by dividing the observed count rate for that chord by the average count rate for chords with a similar geometry (*i.e.* length). This is typically done once a day, usually before the first patient arrives. Once the patient is in position in the camera, a transmission scan is taken, and the attenuation factor for each chord is computed by dividing its transmission count rate by its hoop count rate. The patient is then injected with the isotope, and an emission scan taken, during which time the random count rate is also measured. For each chord the random event rate is subtracted from the emission rate, and the difference divided by the attenuation factor and the chord efficiency. The resulting value is reconstructed, usually with the filtered backprojection algorithm.

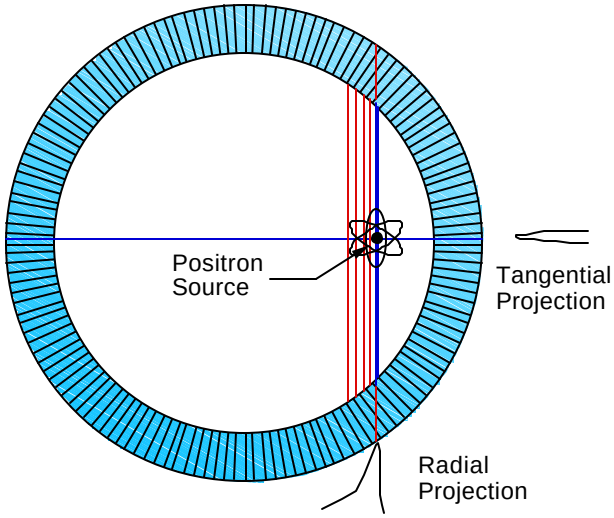
Scattered Events



- **Compton scatter in patient produces erroneous coincidence events.**
- **Can be reduced by rejecting events with E_g < 511 keV.**
- **15% of events are scattered (if tungsten septa used).**
- **50% of events are scattered (if 3-D PET).**
- **Better energy resolution improves Compton rejection.**

A serious problem that *cannot* be corrected for on an chord by chord basis is due to events in which one of the 511 keV photons Compton scatter in the patient, but still interacts in the detector ring. This results in a coincident event, but it is assigned to the wrong chord. This effect can be reduced by rejecting events with photon energies less than 511 keV, but the energy resolution of BGO is poor enough that this is not very effective (a tight energy threshold rejects too many good events, while a loose energy threshold doesn't reject much scatter). Scatter between layers in a multi-layer machine can also be reduced using tungsten septa, and a current research topic is using the emission and attenuation data to predict, and therefore subtract, the scatter contribution to an image.

Radial Elongation



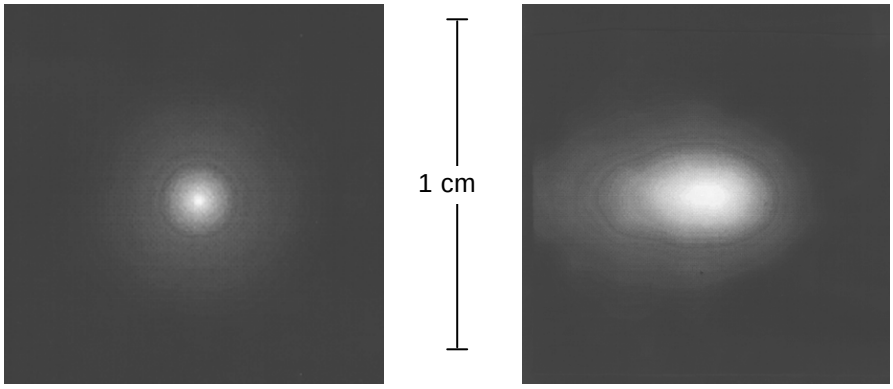
- **Penetration of 511 keV photons into crystal ring blurs measured position.**
- **Blurring worsens as attenuation length increases.**
- **Effect variously known as Radial Elongation, Parallax Error, or Radial Astigmatism.**
- **Can be removed (in theory) by measuring depth of interaction.**

A final problem that affects high resolution tomographs is called radial elongation, and is caused by 511 keV photons penetrating into the detector ring before they interact and are detected. Photons impinging on the face of a crystal at an oblique angle will frequently penetrate and interact in adjacent crystals, which causes the event to be assigned to the wrong chord. The blurring is insignificant near the center of the tomograph ring, but becomes more pronounced the farther the source is from the center. This problem is worse with less dense scintillators such as barium fluoride or sodium iodide. The effect can be removed by measuring the depth of interaction in the scintillator crystal, but few tomographs have yet been built that have this capability.

The combination of the need for high detection efficiency (3 attenuation lengths deep) and this penetration artifact are directly responsible for BGO being the present scintillator of choice for PET. It has the shortest attenuation length of the commonly available scintillators, and so has the smallest penetration artifacts.

Spatial Resolution *Away From* Center

Point Source Images in 60 cm Ring Diameter Camera

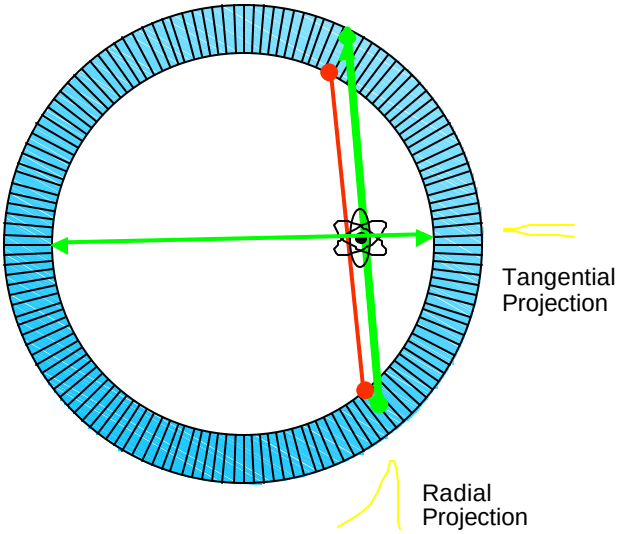


Near tomograph center

14 cm from tomograph center

Resolution degrades *significantly*...

Radial Elongation



- Penetration of 511 keV photons into crystal ring blurs measured position.
- Effect variously known as Radial Elongation, Parallax Error, or Radial Astigmatism.
- Can be removed (in theory) by measuring depth of interaction.

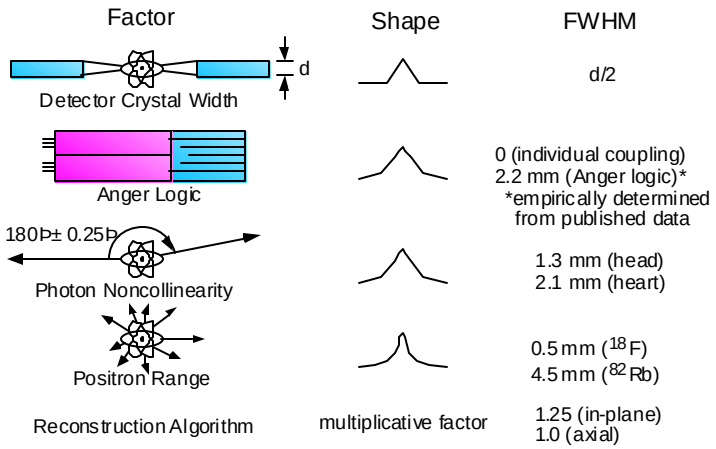
Performance Evaluation

- **Spatial Resolution**
- **Sensitivity**
- **Maximum Count Rate**
- **Temporal Resolution**

I will now define some commonly used measures of PET camera performance and give some *rough* numbers for modern PET cameras.

Spatial Resolution

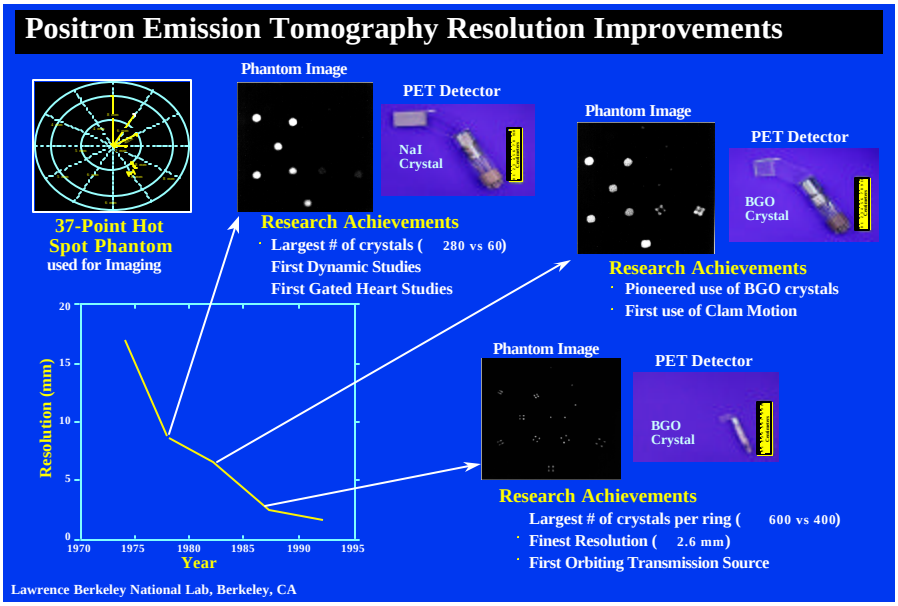
3 mm ==> Excellent
5 mm ==> Good
10 mm ==> Poor



The intrinsic in-plane spatial resolution is mostly determined by the thickness of the scintillator crystal. However, infinitely fine spatial resolution cannot be achieved with infinitely thin crystals – other physical effects such as the photon acollinearity, event mis-positioning in the block detector, positron range, and blurring due to the reconstruction algorithm conspire to worsen the resolution.

The same effects determine the axial resolution, except that it is the crystal height (not thickness) that is the main factor and that the reconstruction algorithm factor is not present.

The spatial resolution in patients is further degraded by patient motion, low statistics, and the partial volume effect (*i.e.* the dimensions of the object vary in the imaged slice).


Positron Emission Tomography Resolution Improvements
37-Point Hot Spot Phantom
used for Imaging
Phantom Image
PET Detector
NaI Crystal
Research Achievements
· Largest # of crystals (280 vs 60)
First Dynamic Studies
First Gated Heart Studies
Phantom Image
PET Detector
BGO Crystal
Research Achievements
· Pioneered use of BGO crystals
· First use of Clam Motion
Resolution (mm)
20
15
10
5
0
1970
1975
1980
1985
1990
1995
Year
Phantom Image
PET Detector
BGO Crystal
Research Achievements
Largest # of crystals per ring (600 vs 400)
· Finest Resolution (2.6 mm)
· First Orbiting Transmission Source
Lawrence Berkeley National Lab, Berkeley, CA

Sensitivity

Detection Efficiency = $\frac{\text{Events / second}}{\mu\text{Ci / ml}}$

Measured by placing a 20 cm diameter phantom with a uniform, known activity concentration into the field of view and measuring the event rate.

30,000 / slice ==> Excellent
20,000 / slice ==> Good
5,000 / slice ==> Poor

The sensitivity is a measure of how efficiently the tomograph detects coincident events, and has units of count rate per unit activity concentration. It is measured by placing a water filled 20 cm diameter phantom in the field of view, mixing a known amount of activity into the water, and measuring the resulting coincident event rate. High sensitivity is desired, as it implies more efficient use of the isotope. Most tomographs have high individual detection efficiency for 511 keV photons impinging on the detector (>90%), so the sensitivity is mostly determined by geometrical factors, that is, the solid angle subtended by the tomograph. As more slices are added, the solid angle coverage increases and you obtain higher system sensitivity. Note that sensitivity is proportional to the square of the slice thickness – not only is the solid angle is proportional to thickness, but the amount of activity in the field of view is also proportional to the thickness.

Noise Equivalent Counts

Sensitivity can be misleading, as it includes Background!

$$\text{Noise Equivalent Counts} = \frac{(\text{True Events})^2}{(\text{True + Scatter + Random Events})}$$

$$\text{Signal to Noise} = 1 / \sqrt{\text{Noise Equivalent Counts}}$$

However, sensitivity is not everything, and can even be misleading because it includes "background" events. A measure that attempts to correct for these background events is the "noise equivalent counts." This measure is the product of "true" events and the contrast, which is defined as the fraction of the total events that are "true." A nice feature of the noise equivalent count measure is that it includes the statistical uncertainties that background processes add and so it obeys counting statistics, that is, its variance is equal to its square root.

If the septa are removed, the solid angle increases and thus the sensitivity increases. However, the scatter and randoms also increase greatly. The noise equivalent count equation assumes that scatter and randoms are subtracted perfectly (and so the only noise they contribute is from the fluctuations about their mean), but scatter is difficult to measure or model accurately. Therefore, the noise equivalent counts is not always an accurate measure of imaging ability either!

Maximum Event Rate

1,000,000 / sec / slice ==> Excellent
100,000 / sec / slice ==> Good
20,000 / sec / slice ==> Poor

- **Maximum rate limited by dead time of scintillators (~1 µs / event).**
- **Block detector designs increase the problem (larger fraction of tomograph is dead after each event).**

The maximum event rate is also quite important, *especially* in septaless systems. Many important tracers have short half-lives, and so all of the events come at once! In addition, it is desireable to take transmission scans as quickly as possible, and so the external source is made as strong as possible. The maximum rate in a single detector crystal is limited by the dead time due to the scintillator fluorescent lifetime (typically 1 µs per event), but as the remainder of the scintillator crystals are alive, this yields an extremely high maximum event rate. In reality, combining crystals together to form groups or blocks reduces the maximum event rate because a greater fraction of the tomograph is dead after each event. Thus, running at the dead time limit (about 1 MHz per module) is common.

Temporal Resolution

1 second ==> Excellent
5 seconds ==> Good
30 seconds ==> Poor

- **Biological activity can change on a short time scale.**
- **Tracer kinetics may contain useful information.**

==> **Need to collect sufficient events to track these changes.**

Finally, the temporal resolution is also important. Some biological processes change on short time scales, and the rate at which they change can give you information about that process. Another advantage of short time resolution is the ability to synchronize the acquisition to a repetitive motion, such as the beating heart, and thus freeze motion that would otherwise blur the image.

Ideal Tracer Isotope

- **Interesting Chemistry**

  Easily incorporated into biologically active compounds.

- **1 Hour Half-Life**

  Maximum study duration is 2 hours.

  Gives enough time to do the chemistry.

- **Easily produced**

  Short half life ==> local production.

There are a limited number of radioactive tracers that can be used for PET. If you could design the ideal isotope, the characteristics that it would have (in addition to positron emission) would be: interesting chemistry (in order to be incorporated into useful drugs), a half-life of about an hour (to give enough time to synthesize the drug, but not so long that the images take forever to acquire), and be easily produced (as the short half-life implies that the isotope must be produce nearby).

There are two main isotope production devices, a cyclotron and a generator. Cyclotrons are expensive to both buy and maintain. A generator is a device in which a parent isotope with a relatively long half-life decays to form a positron emitting isotope with a short half life, which is then chemically separated from the parent isotope. The generator must be periodically re-charged with the cyclotron (or reactor) produced parent isotope, but generators are *much* less expensive and more portable than cyclotrons.

Common Tracer Isotopes

	+ 2 hour half-life.
^{18}F	± Chemically so-so (FDG).
	– Cyclotron produced.
	+ Chemically excellent.
^{15}O, ^{11}C, ^{13}N	– 2 to 20 minute half-life.
	– Cyclotron produced.
	+ Generator produced.
^{82}Rb	– 2 minute half-life.
	– Chemically boring.

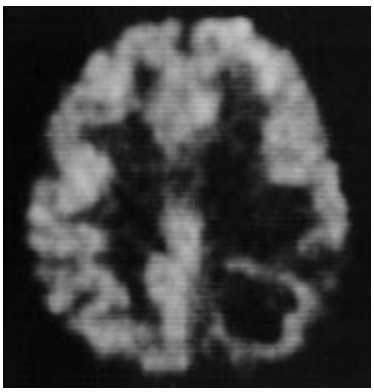
These are the isotopes that are most commonly used. None is ideal, but they are all quite useful. The number of compounds onto which these isotopes are labeled is actually rather limited, but the task of creating and labeling new tracer compounds is a very active (and promising) area of research.

Clinical Uses

- **Brain Dysfunction**
  - **Tumor vs. Necrosis**
  - **Alzheimer's Disease**
  - **Epilepsy**
- **Heart Tissue Viability**
- **Cancer / Oncology**

Finally, we turn to the clinical uses of PET. It is used to image metabolism, so is used mostly to image organs whose size or shape does not tell whether they are functioning, such as the brain or the heart. The disease or dysfunction that you are looking for determines which compound and isotope is used.

Tumor vs. Necrosis



XBB 884-2937

- **Brain tumor patient given radiation therapy.**
- **Symptoms recur.**
- **Too much or too little radiation?**
- **Check with PET.**

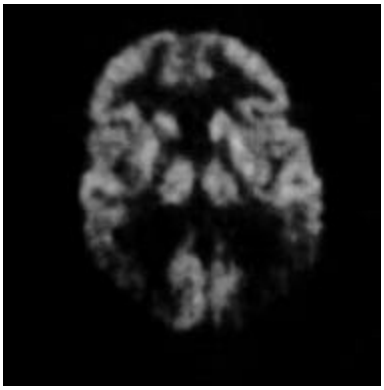
  Too much radiation => dead area.

  Too little radiation => rapid metabolism.

Brains metabolize sugar, so a commonly used agent for measuring brain metabolism is a fluorine labeled sugar analog called FDG (short for fluoro-deoxyglucose). The brain begins to metabolize FDG as if it were sugar, but cannot metabolize it fully, and so it accumulates in the brain tissue rather than being washed out. This property is very helpful, because it means that the tracer becomes concentrated in the tissue rather than being ejected and diffusing throughout the body.

While other modalities (based only on structure) can detect the initial formation of a tumor more easily than PET can, they have difficulty determining if a tumor is responding to treatment. Cancers usually have different metabolic rates than normal brain tissue (higher or lower, depending on the type), so a FDG image can tell you if a tumor is still alive or not. The picture above shows a recurrent tumor, as evidenced by the bright ring of new growth surrounding the dark tumor core.

Alzheimer's Disease

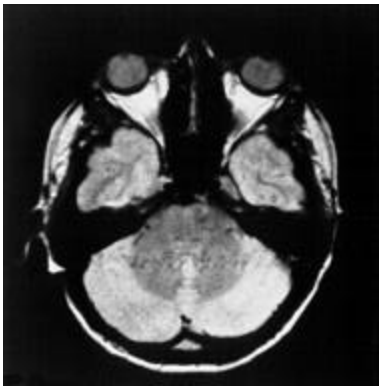


XBB 883-2443

- **Decreased uptake in temporal and parietal regions.**
- **No known cure, but can tell if a curable disease is misdiagnosed as Alzheimer's disease.**

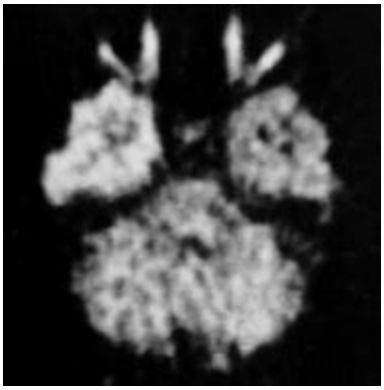
Alzheimer's disease is characterized by decreased metabolism in certain parts of the brain. While there is no known cure for Alzheimer's disease, there are several curable diseases that have similar symptoms, and PET can be used to rule these out. PET can also be used to measure the effect of experimental "cures." The picture above shows a patient with Alzheimer's disease.

Epilepsy



XBB 893-2245A

NMR



PET

- **PET used to identify "focal centers" causing epilepsy.**
- **Focal centers surgically removed.**

The difference between anatomical images and metabolic images is shown by this epileptic patient. The NMR image of an epileptic looks like a normal brain, while the PET image shows an increase in activity in regions that are associated with the epileptic area.

While the actual determination of the "focal centers" that cause the epileptic seizures is somewhat complicated, PET can be used to determine the location of these focal centers, which then can be surgically removed.

Heart Tissue Viability

XBB 875-4265

Dog Heart

- **Patient has heart attack but lives.**
- **Heart *always* sustains some damage.**
- **How badly is the heart damaged?**

  Badly => Coronary bypass.

  Not Badly => No surgery.
- **PET measures *degree* of damage.**

The ability to quantitatively measure metabolism is vital when imaging heart attack patients. There is always *some* damage after a heart attack; PET tells you *how much* damage and whether the damaged tissue has any hope of recovering. This knowledge can then be used to determine whether or not to perform bypass surgery, which is probably one of the most important potential routine clinical applications for PET.

The image above is actually of a dog heart, which is roughly 5 cm across. The bright, horseshoe shaped region is the wall of the left ventricle, which is the chamber that pumps the blood through our body. This image is of a healthy dog – a diseased area would show up as a dark spot on the horseshoe.

Motion compensation

• The heart moves significantly within the chest cavity during cardiac and respiratory cycles

• This leads to inconsistency in the projection data

• As a consequence, reconstructed images of the myocardium appear blurred

• Usually, cardiac PET studies are time **gated** using the electrocardiogram and chest strap strain gauge sensors

• Projection data obtained at **corresponding time points on successive cycles** are reconstructed separately.

• What is the disadvantage of this approach?

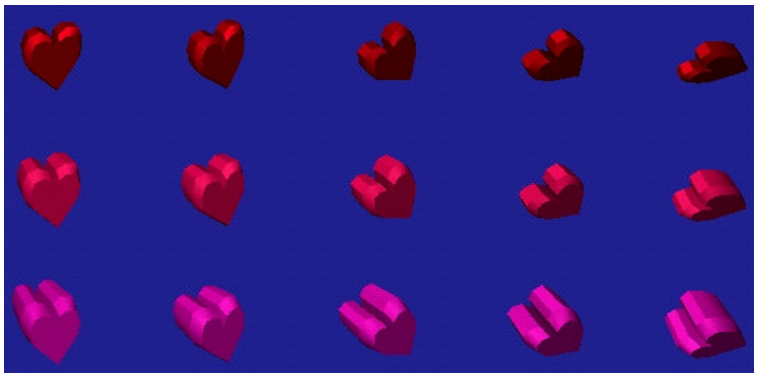
Double Gating

Respiratory Phases

~ rigid motion (translation + rotation)

Cardiac Phases

Non-rigid motion (contraction)



Slide courtesy Greg Klein, LBNL

One important aspect of this is that none of the data has been thrown away. The challenge once we have successfully stopped the motion is to find a way to recombine all these individual reconstructions in such a way that motion blur is not re-introduced.

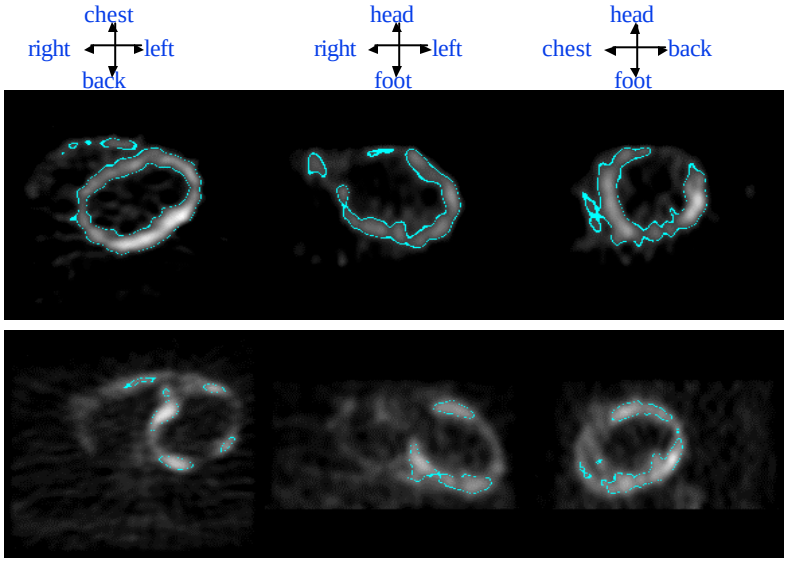
Motion compensation

• This problem can be ameliorated by applying geometric transformations to the separate gated images so that these all correspond to the geometry of the myocardium at a specific point of the cycle

• Respiration is easily accounted for by translating the heart in space

• Ventricular contraction requires a non-rigid transformation. The specific transformation may be obtained using real time magnetic resonance imaging, or from a mechanical model of the heart

Extent of Respiratory Motion



Subject 1
11.2 mm
(1.4,1.0,11.1)

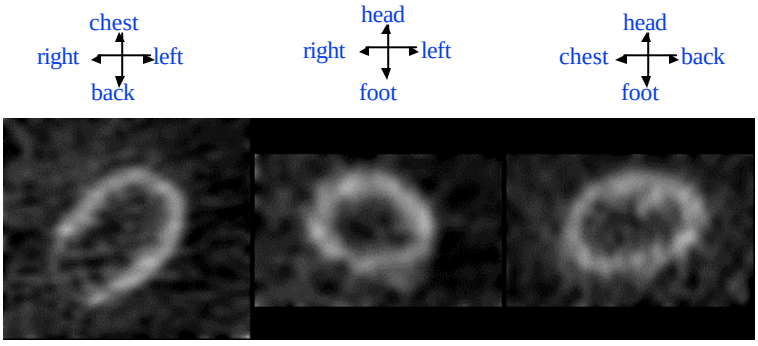
Subject 2
13.8 mm
(-2.2,-2.9,13.3)

Transverse Coronal Sagittal

Slide courtesy Greg Klein, LBNL

Extent of Contractile Motion

Base moves 9-14 mm towards apex
Walls thicken from 10 mm to 16 mm

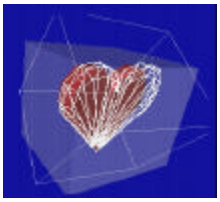


Transverse Coronal Sagittal

Slide courtesy Greg Klein, LBNL

Motion Compensation

Reference
Image Volume



Composite Sum
less noise, less blur

Target
Image Volume

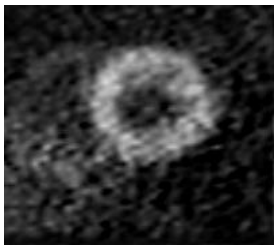
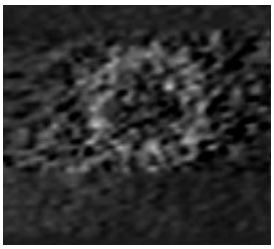
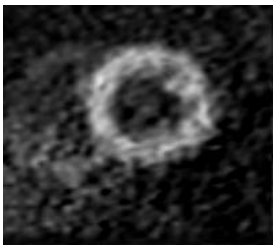
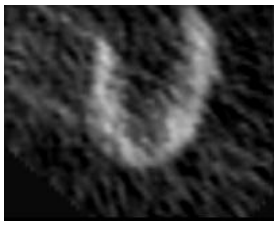
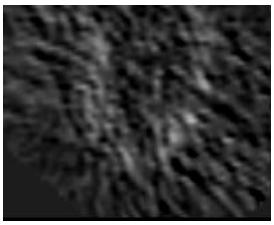
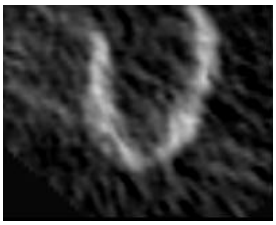
Registration

Registered
Target

Image Space
Summing

Slide courtesy Greg Klein, LBNL

Contractile Compensation Results

Short Axis

Long Axis

Ungated Sum
(motion blur)

Single Time Frame
End-Diastole
(noisy)

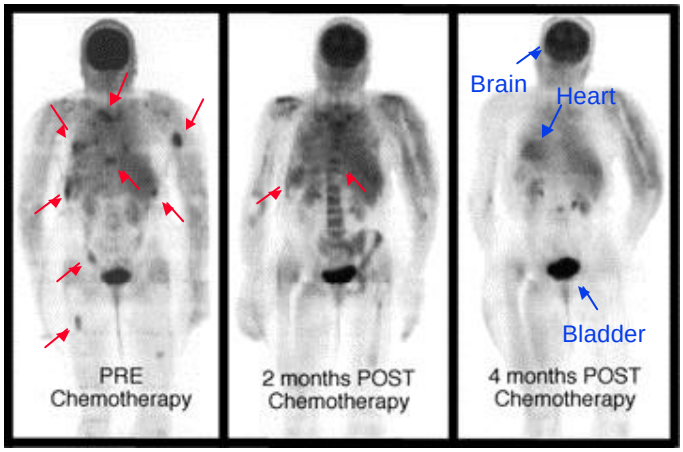
Motion Compensated
Gated Sum

Slide courtesy Greg Klein, LBNL

Slide courtesy Greg Klein, LBNL

Cancer / Oncology

Metastases Shown with Red Arrows



Normal Uptake in Other Organs Shown in Blue

- **Many tumors have higher than normal uptake.**
- **Image the whole body to find metastases.**

Many types of cancer, including breast cancer, have a significantly higher uptake of FDG than either normal tissue or benign tumors do. This property allows PET to screen patients for tumors, search for metastases (which are difficult to see with other modalities, since they are small and can occur anywhere in the body), and evaluate the effect of treatment (since it provides information on metabolism).

The three images above show the response of a breast cancer patient to chemotherapy. Before therapy, metastases are visible in the axillary (armpit) and mediastinal (center of the chest) nodes, as well as in the lung. Two months after chemotherapy was begun, all tumors are in remission except the one in the lung. After four months of chemotherapy, all tumors are in remission. The other visible objects in these images are the brain, the bladder, and the heart.

These images were obtained with a technique known as the whole body scan. A multi-slice (24 plane) PET camera with a large axial field of view (15 cm) is used, and the patient is imaged in several 15 cm thick sections. To save time, transmission data is not collected, so these images are not corrected for attenuation. The "gray scale" is opposite from the previous images — regions of large uptake appear dark and regions of low uptake appear light.

Further Reading

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Special Issue on Clinical PET, Journal of Nuclear Medicine Vol. 32, pp. 561–748, 1991.

Moses WW, Derenzo SE and Budinger TF. *PET detector modules based on novel detector technologies*. Nucl. Instr. Meth. A-353: pp. 189–194, 1994.

http://www.nuc.ucla.edu/html_docs/frame_pet.html "Let's Play PET", an outstanding tutorial from UCLA covering many instrumentation and clinical aspects of PET.

http://www.ami-imaging.org/public/icp Web site for the Institute for Clinical PET, which is concerned with clinical acceptance for PET.

The Sandler book has good sections on PET and SPECT, as well as sections on the clinical aspects. The Derenzo article is hardware oriented, and has remained surprisingly current. The Moses article is also hardware oriented. The other references include some hardware, but tend to focus on the clinical and medical research uses of PET. While not listed above, there was a seven part series of review articles (from 1979 to 1986) in the Journal of Computer Assisted Tomography whose titles began with *"Quantitation in Positron Emission Computed Tomography"*. All had either E. J. Hoffman or M. E. Phelps as one of the authors. Finally, I hesitate to put down websites as references due to their volatility, but the "Let's Play PET" http://www.nuc.ucla.edu/html_docs/frame_pet.htmlweb site is extremely informative and well worth the visit.

Thanks To:

Stephen Derenzo,
Lawrence Berkeley Laboratory

Greg Klein

Lawrence Berkeley Laboratory

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Franklin McLean Institute

PET Applications: Case Study

Gene Therapy for the Treatment of Parkinson's Disease

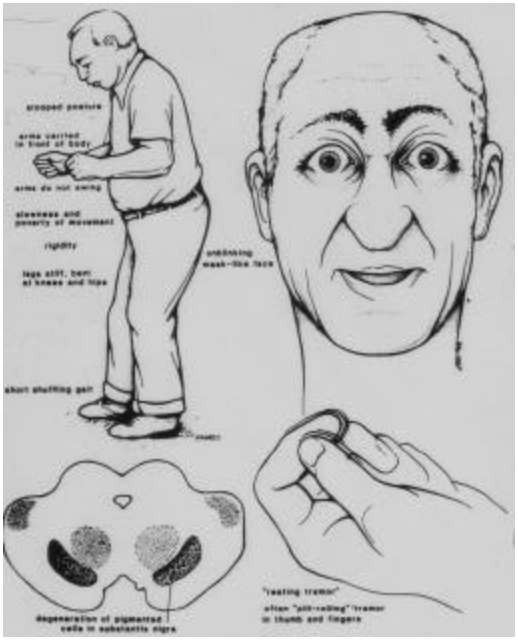
Preclinical Studies in a Primate Model

Parkinson's Disease

Progressive neurodegenerative disease

Movement disorder:
- **tremor**
- **slowness of movement**
- **difficulty initiating movement**
- **rigidity**
- **stiffness**
- **impaired balance & coordination**

Degeneration of dopamine producing cells in the substantia nigra



MPTP

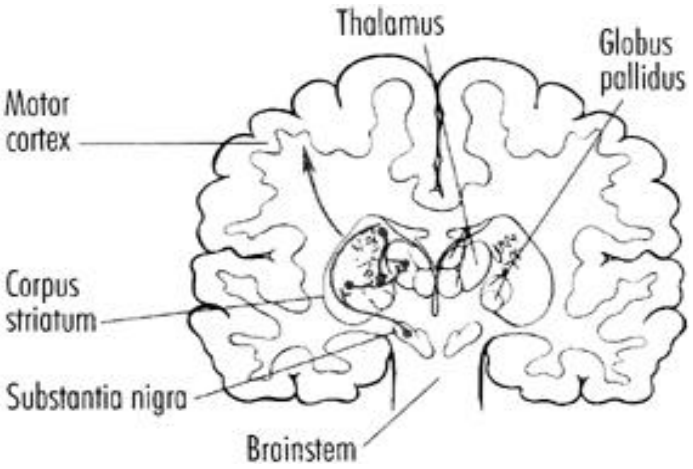
1-methyl, 4-phenyl,1,2,3,6-tetrahydropyridine

Neurotoxin that produces Parkinsonian syndrome

So-called frozen addicts posed together in 1991, after having received treatment. Nine years earlier all suddenly became immobile, as if they had instantly acquired Parkinson's disease, after taking heroin containing an impurity, MPTP. Studies of how MPTP led to the freezing has generated many insights into the biochemical reactions that could contribute to a more classical presentation of the disease.

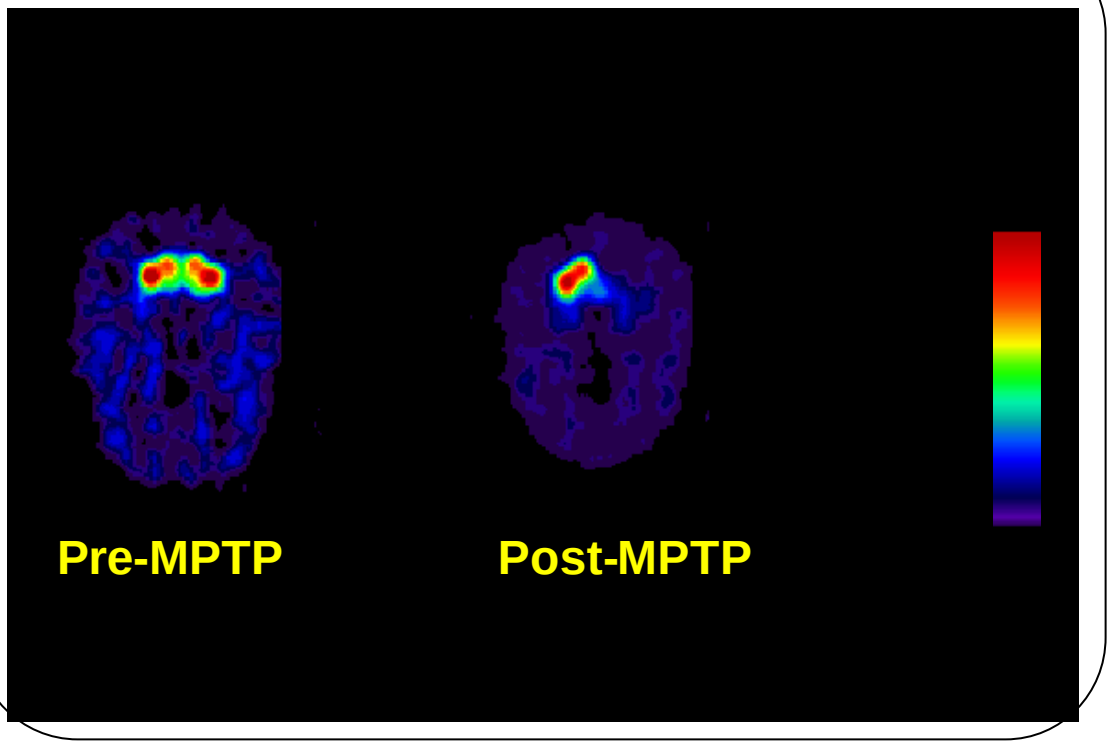
Both PD and MPTP

Degeneration of nigrostriatal pathway

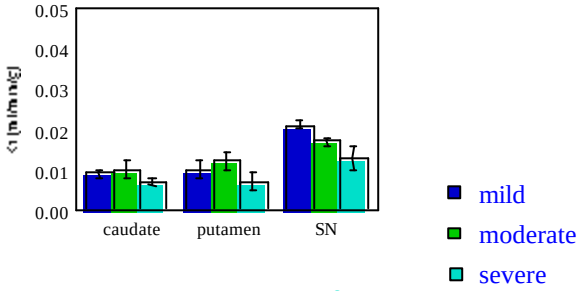


MPTP Primate Model of Parkinson's Disease

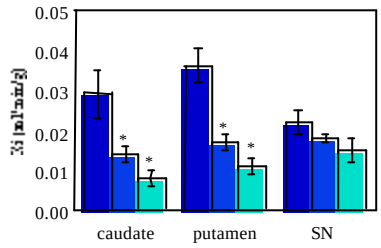
- **Large brain**
- **Surgical parameters evaluated in monkeys can be applied to humans**
- **Neuroimaging (PET, MRI)**
- **Clinically relevant animal model of Parkinson's disease**

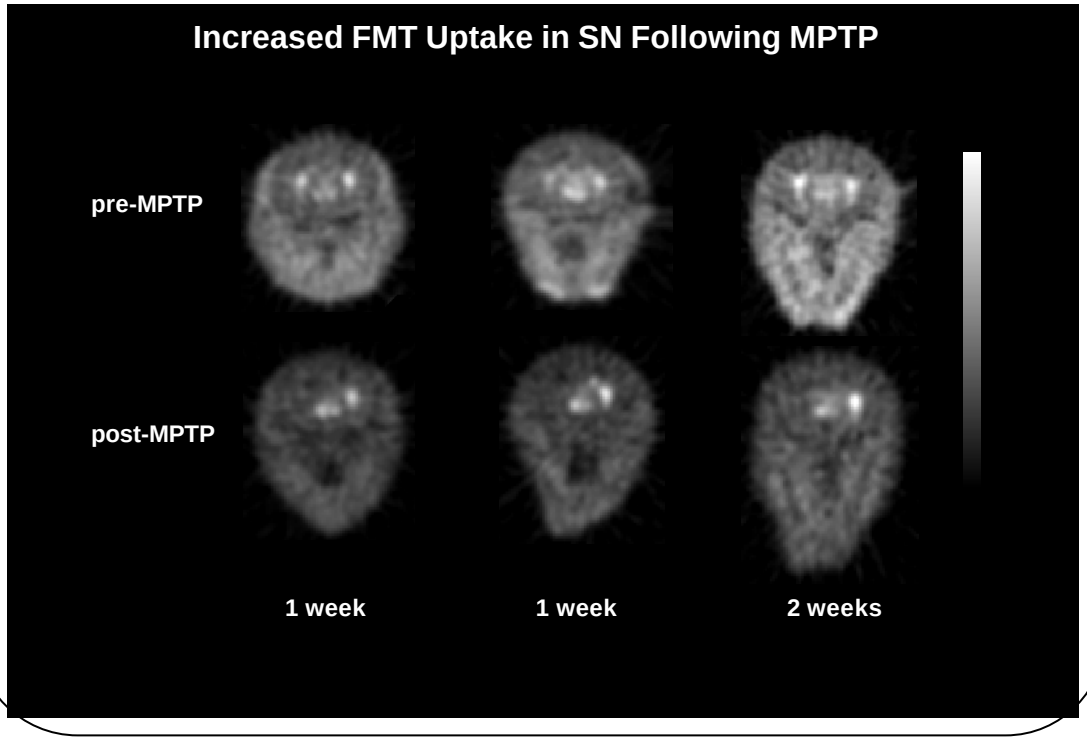

Pre-MPTP
Post-MPTP

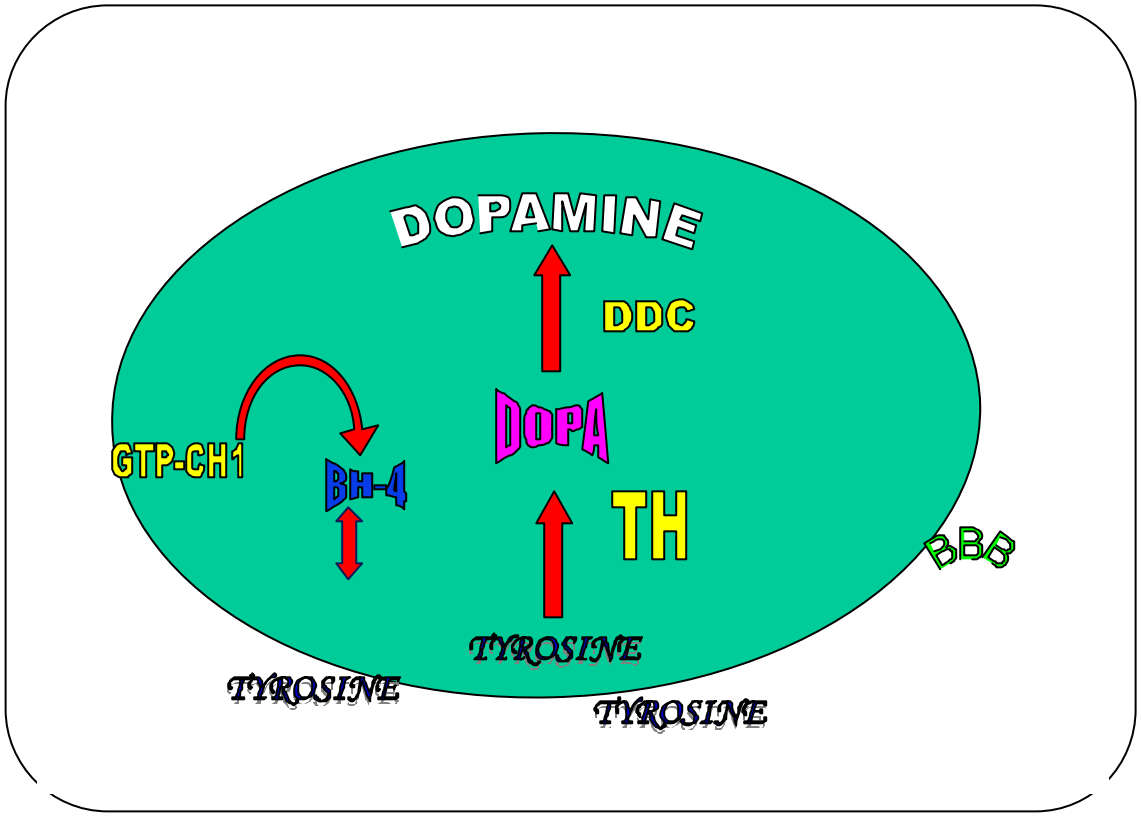
Side of MPTP Infusion

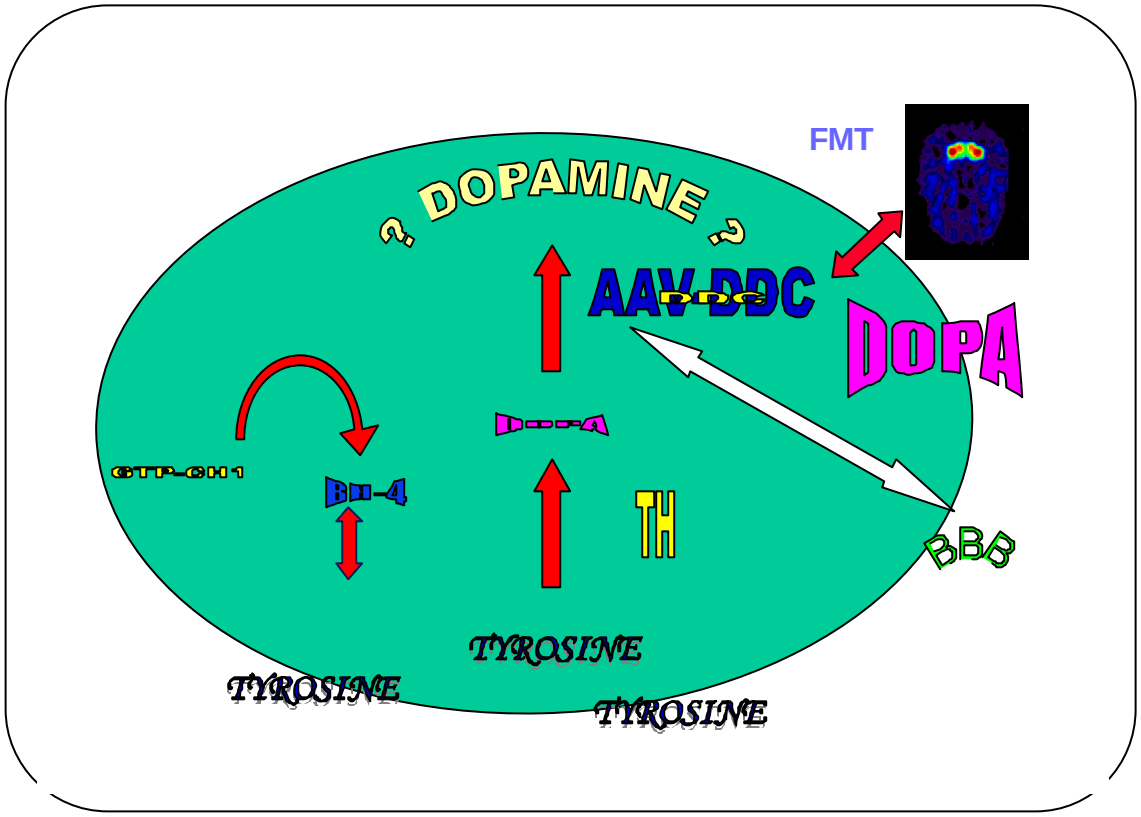


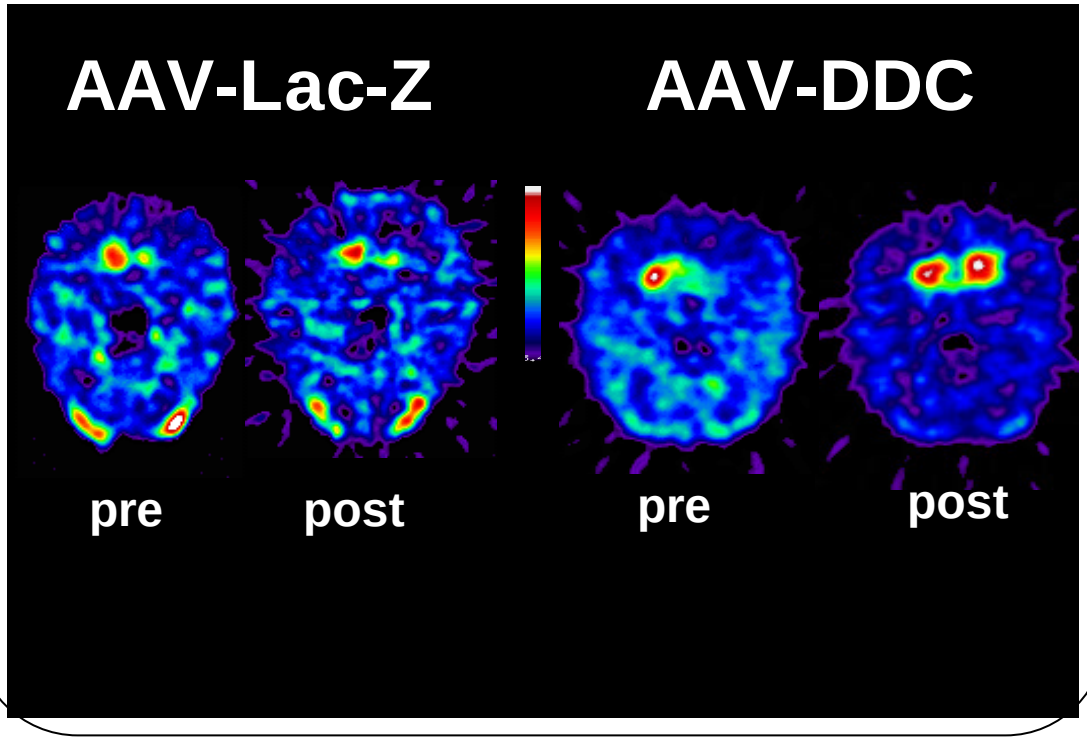
Side Opposite MPTP Infusion

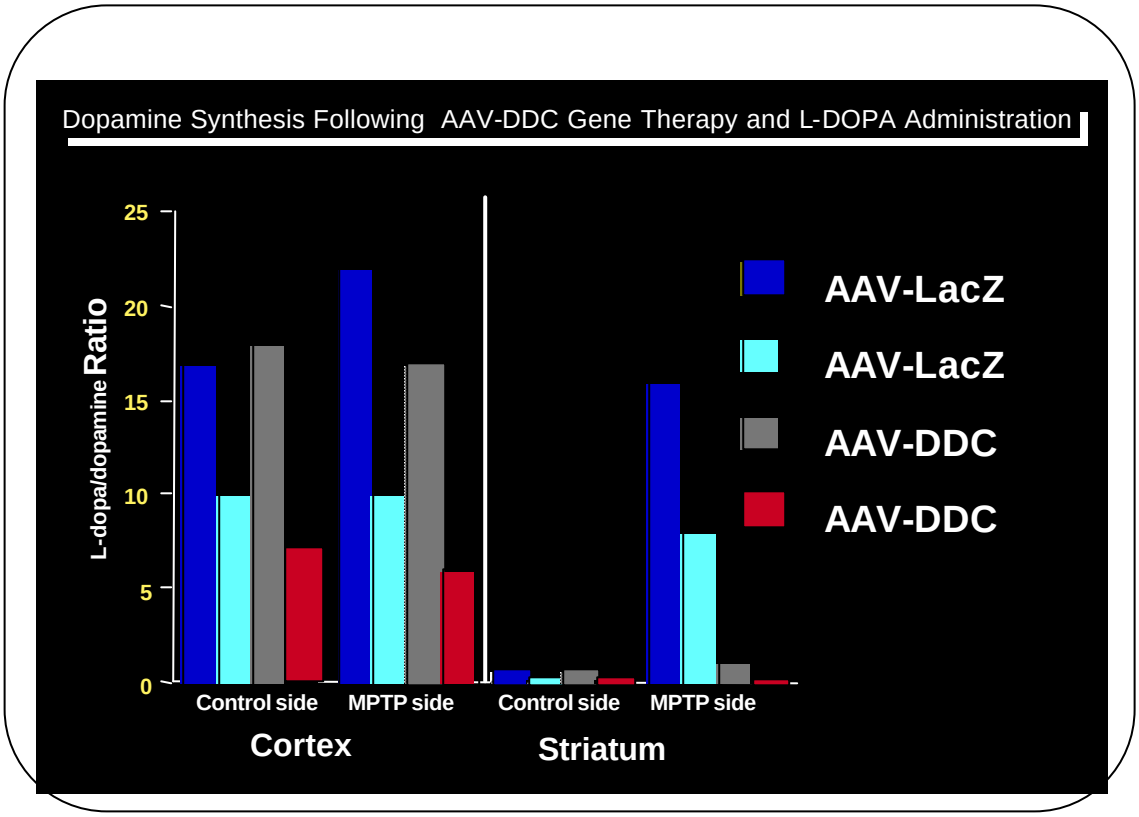



Increased FMT Uptake in SN Following MPTP
pre-MPTP
post-MPTP
1 week
1 week
2 weeks


DOPAMINE
DDC
DOPA
TH
GTP-CH1
BH-4
BBB
TYROSINE
TYROSINE
TYROSINE


FMT
? DOPAMINE ?
AAV-DDC
DDC
DOPA
GTP-CH1
BH-4
TH
BBB
TYROSINE
TYROSINE
TYROSINE


AAV-Lac-Z
AAV-DDC
pre
post
pre
post


Dopamine Synthesis Following AAV-DDC Gene Therapy and L-DOPA Administration
L-dopa/dopamine Ratio
25
20
15
10
5
0
Control side
MPTP side
Control side
MPTP side
Cortex
Striatum
AAV-LacZ
AAV-LacZ
AAV-DDC
AAV-DDC

Conclusions

- **Restoration of DA activity by gene therapy approach with single gene (DDC)**
- **Stable DDC gene expression (more than 24 months)**
- **Pro-drug approach for safe and local delivery of dopamine**
- **Significant clinical improvement following AAV-DDC gene transfer**
  - **Separation of Rx response to L-dopa and side effects (wider Rx window)**
- **In-vivo imaging can be used for detection of gene expression**

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